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AQUEOUS PHARMACEUTICAL PREPARATION

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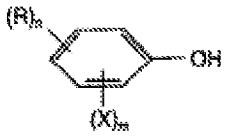
CLAIMS:

1. An aqueous preparation which comprises an active ingredient, cyclodextrin and a compound of the formula:



wherein R is alkyl, X is halogen, n is an integer of 0 to 2 and m is an integer of 0 to 3.

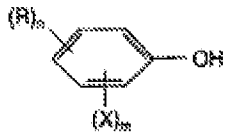
Detailed Description of the Invention

This invention relates to a pharmaceutical composition which comprises an active ingredient, cyclodextrin and a preservative, and its production.

It is generally known that drugs which are strongly hydrophilic but have a small oil/water partition coefficient are poorly absorbable from the gastrointestinal tract and therefore are poor in bioavailability. Accordingly, such hydrophilic drugs are administered in the form of an injection-so as to make their efficacy manifest to a satisfactory extent. However, administration by injection is entrusted only to experts and is accompanied by pain in patients. Therefore, a development of a preparation, other than an injection, which is capable of affording a high bioavailability and is applicable in an easy manner, has been desired. As a result of a study made for the purpose of increasing the bioavailability of such drugs being poorly absorbable from the gastrointestinal tract so as to make their pharmacological effects manifest in an efficient manner, it was found that addition of cyclodextrin to preparations other than an injection causes a significant increase in absorbability of the drugs and that addition of cyclodextrin to preparations containing other drugs than those mentioned above also results in improvement in the stability and solubility of active ingredients. Then, the present inventors prepared aqueous preparations containing active ingredients and cyclodextrin and added preservatives thereto. Regrettably, however, a phenomenon that the preserving effect of the preservative added is decreased was observed in some of such aqueous preparations.

Under these circumstances, the present inventors conducted an intensive study to find out an aqueous preparation which contains an active ingredient, cyclodextrin and a preservative but does not show a decrease in the preservative effect and found that this object can be achieved by the use of phenol derivatives as preservatives. Continued research based on this finding has now led to completion of the present invention.

The invention thus provides an aqueous preparation which comprises an active ingredient, cyclodextrin and a compound of the formula:



wherein R is alkyl, X is halogen, n is an integer of 0 to 2 and m is an integer of 0 to 3.

The alkyl represented by R in the compound (I) to be contained in the aqueous preparation according to the invention preferably contains 1 to 8 carbon atoms.

Examples are methyl, ethyl, n-propyl, n-butyl, n-amyl, n-hexyl, n-heptyl and n-octyl, among others.

The halogen represented by X is, for example, chlorine or bromine.

Examples of the compound (I) to be used in accordance with the invention are phenol, o-ciesol, m-ciesol, p-ciesol, o-chlorophenol, m-chlorophenol, p-chlorophenol, o-bromophenol, m-bromophenol, p-bromophenol,

2,4-dichlorophenol, 2,4, 6-trichlorophenol, 2,4,6-tribromophenol, p-chloro-m-cresol, p-bromo-m-cresol, 2-n-butyl-pchlorophenol, 2-n-amyl-p-bromophencl, p-chloro-m-xylenol, p-bromo-m-xylenol , amongst others.

The active ingredient in the aqueous preparation according to the present invention is not limited to any specific class. Thus, said active ingredient includes, among others, physiologically active polypeptide drugs, polysaccharide drugs, aminoglycoside drugs, beta-lactam antibiotics, nucleic acid drugs and other hydrophilic drugs and various lipophilic drugs.

The cyclodextrin to be used in the aqueous preparation according to the invention includes various cyclodextrin species obtained by hydrolysis of starch with an acid or amylase and, in addition, cyclodextrin derivatives.

Said cyclodextrin species include α-cyclodextrin (polymerization degree: 6), β-cyclodextrin (polymerization degree: 7) and γ-cyclodextrin (polymerization degree: 8) [cf. Biochemical and Biophysical Research Communications vol. 5, pages 11-15 (1961), Farumashia, Vol. 16, No. 1, pages 33-37 (1980); Yakugaku Zasshi (Journal of the Pharmaceutical Society of Japan), Vol. 101, No. 10, pages 857-873 (1981), Japanese Patent Application Publication Sho. 53(1978)-31,223].

Said cyclodextrin derivatives include, among others, tri-O-methylcyclodextrin [cf. Chemical and Pharmaceutical Bulletin, Vol. 28, pages 1552-1558 (1980)] and triaminocyclodextrin [cf. Angewandte Chemie, International Edition in English, Vol. 19, pages 344-362 (1980)].

The aqueous preparation according to the invention may take the form of liquid preparations for injection, liquid preparation for internal use (e.g. extracts, elixirs, syrups, infusions, decoctions, suspensions, emulsions, aromatic waters, lemonades, fluid extracts), liquid preparations for external use (e.g. eye drops, aqueous preparations for rectal administration, aqueous preparations for vaginal administration, aqueous ointments, nasal drops, ear drops, cataplasms, liniments, lotions), etc.

The aqueous preparation according to the invention contains water in an amount of from 10 to 99.9 percent (weight by volume), preferably from 20 to 99 percent (weight by volume).

The aqueous preparation can be produced by any of the per se known methods. Thus, for instance, an injection can be produced by dissolving an effective amount of the active ingredient and cyclodextrin in distilled water for injection, further adding an isotonizing agent, a buffer and the preservative according to the invention and, after complete dissolution, filtering the solution through a Millipore filter (Millipore Corporation, USA), followed by filling the filtrate into vials, sealing the vials and high-pressure steam sterilization at 115.50C for 30 minutes. The injection may contain a stabilizer, a solubilizing agent and/or a local anesthetic, for instance, in addition to the above-mentioned components.

A liquid preparation, for instance a syrup, can be produced by adding an effective amount of the active ingredient, cyclodextrin, a thickening agent (e.g. sodium carboxymethyl cellulose, methyl cellulose), sucrose, a flavoring agent, etc. to a simple syrup or water with the preservative according to the invention dissolved therein in advance, followed by stirring for homogenization and adjusting the volume with water.

A liquid preparation for external use, for example a nasal drop preparation, can be produced by adding an effective amount of the active ingredient, cyclodextrin, an isotonizing agent, a buffer, a flavoring agent, etc. to an aqueous solution of the preservative according to the invention and, after complete dissolution, filtering the solution and filling the filtrate into containers for nasal application.

The concentration of cyclodextrin in the preparation is generally 0.1 to 50 percent (weight by volume), preferably about 0.5 to 20 percent (weight by volume), more preferably about I to 10 percent (weight by volume).

The phenol derivative (I) is used in the aqueous preparation according to the invention in a concentration not lower than the minimal concentration required to inhibit the growth of microorganisms (MIC, minimal inhibitory concentration), preferably in a concentration of from 0.001 to 1 percent (weight by volume), more preferably from 0.01 to 1 percent (weight by volume).

A characteristic feature of the invention lies in that the preservative is added for the purpose of guaranteeing, for a long period of time, the quality of aqueous preparations with cyclodextrin being incorporated therein so as to stabilize the active ingredient, improve the solubility and increase the bioavailability,and for other purposes. The use of the preservative according to the invention does not result in decreases in antimicrobial activity due to interaction with cyclodextrin and does not result in precipitation of an insoluble complex; hence,the use of the present preservatives can give effective aqueous preparations.

The following Experimental Examples and Examples illustrate the invention in more detail. In the following description, "percent (percent)" means "weight/volume percent" unless otherwise specified.

Experimental Example 1

Various preservative solutions are tested for the minimal inhibitory concentration (MIC) using Aspergillus niger ATCC 9642 (A. niger) and Escherichia coli IFO 3044 (E. coli) as the test organisms. Thus, two culture media are prepared by adding 0 percent and 5 percent of a-cyclodextrin, respectively, to a 1/15 M phosphate buffer (pH 6.5) containing 2 percent of Polypeptone (Daigo Nutritive Chemicals Ltd., Japan). The preservative is added to each medium and the resulting solution is diluted serially with each of the respective media to give solutions differing in preservative concentration. The test organisms are added to these solutions to a final concentration of 105 cfu/ml

(cfu: colony forming unit). After incubation at 25 °C (when A. niger ATCC 9642 is used) for 5 days or 35 °C

(when E. coli IFO 3044 is used) for 3 days, the minimal inhibitory concentration is measured by observation with the naked eye. The results obtained in this manner are shown in Table 1.

Table 1 Minimal inhibitory concentration (MIC, g/ml)

Culture	Culture medium		Culture medium + 5% alpha-cyclodextrin medium	
test organisms	niger ATCC 9642	E. coli IFO3044	niger ATCC 9642	E. coli IFO3044
Preservative	Micro g/ml	Micro g/ml	Micro g/ml	Micro g/ml
Control				

Methylparaben	500	500	4000	4000
Ethylparaben	250	500	4000	4000
Propylparaben	125	250	4000	4000
Butylparaben	125	125	4000	4000
The present invention				
Phenol	-	1000	-	2000
p-Chlorophenol	200	200	400	400
p-Chloro-m-cresol	100	200	200	200
p-Chloro-m-xylenol	50	100	75	150

As is evident from Table 1, the parabens used as controls (methylparaben, ethylparaben, propylparaben and butylparaben) each show a significant increase in the value of minimal inhibitory concentration in the cyclodextrincontaining culture medium, hence a significant decrease in the antimicrobial activity. On the other hand, the preservatives according to this invention each exhibit only a slight decrease in the antimicrobial activity even in the cyclodextrin-containing culture medium.

Experimental Example 2

An aqueous solution containing 5 percent ofα-cyclodextrin or 1 percent ofβ-cyclodextrin was prepared and each of various preservatives was dissolved therein. After standing in a cold place overnight, the solution was examined for the presence or absence of a precipitate. The results obtained are shown in Table 2.

Preservative	Concentration	5% alpha-cyclodextrin	1% beta-cyclodextrine
Control			
Metylparaben	0.5	++	++
Propylparaben	0.1	+	+
Benzalconium Chloride	0.03	+	+
Benzathonium Chloride	0.03	+	+
Chlorbutanol	0.3	++	++
Chlorhexidine gluconate	0.1	**	++
Benzyl alcohol	0.5	+	+
Phenethyl alcohol	0.1	+	+
Cetylpyridinium chloride	0.03	+	+
The present invention			
Phenol	0.1	-	-

p- cresol	0.05	-	-
O- cresol	0.05	-	-
m- cresol	0.05	-	-
p-chlorophenol,	0.05	-	-
p-chloro-m-cresol,	0.02	-	-
p-chloro-m-xylenol	0.02	-	-

Notes: -, no precipitation; + precipitation; ++, precipitation in a large amount.

As is evident from Table 2, a precipitate forms in cyclodextrin-containing solutions with each of the preservatives used as controls. On the other hand, the preservatives according to the invention give no precipitate. Therefore, it is considered that the interaction between the preservatives used in this invention and cyclodextrin is slight and accordingly does not result in a decrease in the antimicrobial activity.

Example 1

A preparation for nasal application by dropping is produced by dissolving 5 g ofα-cyclodextrin and 1.8 g of glycerol as an isotonizing agent in 80 ml of purified water, heating the solution to 80 °C, adding 30 mg of p-chloro-m-xylenol as a preservative and 10 mg of l-menthol as a flavor at that temperature, cooling, after complete dissdlution, to 25 °C, adding 5 g of leuprolide [TAP-144: (Pyr) Glu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NHCH2-CH3 (abbreviations for amino acids being by IUPAC-IUB Commission on Biochemical Nomenclature), and, after dissolution, further adding purified water to make 100 ml.

Example 2

A preparation for nasal application by dropping is produced by completely dissolving 5 g of α-cyclodextrin, 5 g of protirelin [thyrotropin releasing hormone (TRH): L-pyroglutamyl-L-histidyl-L-prolinamide] tartrate, 600 mg of sodium chloride and 20 mg of p-chloro-m-xylenol as a preservative in 100 ml of purified water.

Example 3

A preparation for nasal application by dropping is produced by completely dissolving 100 mg of fertirelin acetate, 1 g of β-cyclodextrin, 800 mg of sodium chloride and 50 mg of p-chloro-m-cresol as a preservative in 100 ml of purified water.

Example 4

A hydrogel eyedrop is produced by adding 634 mg of β-cyclodextrin and further 50 mg of 2,4-dichlorophenol as a preservative to 200 mg of indomethacin and 117 mg of L-arginine, adding distilled water to make the whole amount 100 ml, adding 2 g of methylcellulose (4,000 cp) thereto and stirring the mixture under ice cooling.

Example 5

An injection is produced by dissolving 10 mg of prostaglandin, 150 mg of α-cyclodextrin and 100 mg of p-bromophenol as a preservative in 100 ml of distilled water for injection and filling the solution into vials, followed by high-pressure steam sterilization at 115.5 °C for 30 minutes.

Example 6

A suspension for internal application is produced by adding 100 g ofβ-cyclodextrin, 500 mg of 2-n-amyl-p-bromophenol as a preservative and 500 ml of purified water to 10 g of 1-(2-tetrahydrofuryl)-5-fluorouracil, followed by mixing.

Example 7

A syrup for internal application is produced by adding 20 ml of water to 10 g of nalidixic acid and 5 g ofβ --cyclodextrin, mixing well, adding 0.8 g of sodium carboxymethylcellulose, 2 ml of ethanol and 60 ml of simple syrup, further dissolving 50 mg of p-cresol as a preservative and making the whole volume 100 ml.

Example 8

An injection is produced by dissolving 5×10^3 units of γ-interferon, 100 mg of β-cyclodextrin, 80 mg of sodium chloride and 50 mg of phenol as a preservative in 10 ml of distilled water for injection and, after sterile filtration, filling the solution into 1-ml vials.